Pregnancies after Chemotherapy of Trophoblastic Neoplasms

Abstract. *We have analyzed 88 pregnancies in 50 women who had previously been treated for gestational trophoblastic neoplasms with chemotherapeutic agents. No increase in fetal wastage, congenital abnormalities or complicated pregnancies was noted, suggesting that these drugs do not damage human oocytes in the doses and time periods used. The possibility that recessive mutations have been induced but were undetected cannot be evaluated definitively at present.*

Many cytotoxic agents useful in chemotherapy of neoplasms are teratogenic in animals and humans receiving these drugs early in pregnancy (*1*). Although the use of these substances has increased in young women, there are few data concerning the effects of these agents on mammalian oocytes and possible hazards to mother and fetus in a subsequent pregnancy. We have therefore reviewed the reproductive performance of all patients who had been treated successfully for gestational trophoblastic neoplasms at the Clinical Center, NIH, between January 1956 and 1 January 1969. Of these, there were 91 women with intact ovaries and uterus. Each of these 91 women was questioned about pregnancies after treatment for neoplasms and permission was obtained to request medical data from physicians who cared for them during pregnancies. Their physicians replied in every instance either by letter or telephone and their cooperation has contributed immeasurably to the completion of this study.

Cytotoxic agents used and dosage schedules were as follows:

Single agents:

1) methotrexate, 20 to 25 mg/day intramuscularly for 5 days;

2) actinomycin-D, 8 to 10 μg/kg per day intravenously for 5 days;

3) vinblastine, 2 to 5 mg twice daily intravenously for 3 days;

4) nitrogen mustard, 0.4 mg/kg intravenously, one time;

5) 6-diazo-norleucine, 15 to 30 g/day orally for 33 days;

Multiple agents:

1) actinomycin-D, 10 μg/kg per day intravenously for 5 days, and chlorambucil, 10 mg/day orally for 5 days;

2) methotrexate, 20 to 25 mg/day intramuscularly for 5 days, actinomycin-D, 8 to 10 μg/kg per day intravenously for 5 days, and chlorambucil, 10 mg/day orally for 5 days.

Details of treatment regimens including methods used for monitoring response, and criteria for diagnosis and maintenance of remission have been described (*2*).

Of the 91 women studied, 38 had metastatic neoplasms and 53 had trophoblastic tissue apparently confined to uterus and pelvis. Fifty of these women conceived subsequently.

Of the 41 women who did not subsequently conceive, 10 used oral or mechanical contraceptives. Four had reasonable gynecologic basis for infertility and 27 had no studies relevant to infertility.

The 50 women conceiving have had 88 pregnancies which terminated with 71 live full-term infants (81 percent), 15 spontaneous abortions (17 percent), and 2 stillbirths (2 percent). The ages of the 71 live children range from 1 to 10 years.

Cumulative dosages of drugs received were compared between women who conceived and those who failed to conceive. Results are shown in Tables 1 and 2. The apparent minor trend relating fertility to cumulative dose of chemotherapy in Table 1 is not borne out when the total experience in Tables 1 and 2 is considered. The patient who received the most chemotherapy, consisting of eight courses of methotrexate, six courses of actinomycin-D, three courses of triple therapy, and one course of 6-diazo-norleucine (33 days), as well as 2200 r of whole-brain irradiation, has had two normal pregnancies and two normal children.

The 17 abortions plus stillbirths reported occurred in 13 women, with two women each having a total of three spontaneous abortions. No correlation between amount of chemotherapy and fetal wastage is apparent (Table 3).

The complications in addition to fetal wastage experienced by the entire group of 50 women in a total of 88 pregnancies included: fluid retention requiring diuretics in two (2.4 percent), bleeding probably due to partial placental abruption in two (2.4 percent), hyperemesis gravidarum in one (1.4 percent) and postpartum hemorrhage in five (5.7 percent) due to placenta accreta in three (3.4 percent).

The products of these pregnancies were normal with the exception of one child with Pendred's syndrome (the only abnormal child of the patients with metastatic disease), one child with tetralogy of Fallot, and one child with multiple hemangiomata, eczema, and strabismus. A stillborn child was found without an anterior abdominal wall and with numerous other congenital anomalies. None of the abortions or other stillborns were noted to have gross abnormalities.

The existence of a group of women who had received chemotherapeutic agents prior to conception offered the unique opportunity to examine the effects of these agents on the human oocyte. The results of pregnancy in untreated women are well documented by Stickle (*3*) and Bierman *et al.* (*4*), who reported that 30 percent of all conceptions are either aborted or stillborn. In our small group the combined fetal morbidity was 19.5 percent. Bierman reported that 30 percent of stillborns had congenital defects and one of the two stillborn infants of our patients had multiple congenital defects. Bierman also noted that by age 2 years, 21 per-

Table 1. Single agent treatment.

Cumulative dose (mg)	Conceiving (No.)	Not conceiving (No.)	Total
Methotrexate			
100 to 250 mg (1 to 2 courses)	18	7	25
250 to 500 mg (3 to 4 courses)	21	16	37
> 500 mg (5 or more courses)	3	5	8
Actinomycin			
	1	2	3
Totals	43	30	73

Table 2. Multiple agent treatment.

Cumulative dose		Conceiving (No.)	Not conceiving (No.)
Methotrexate (mg)	Actinomycin (μg/kg)		
100 to 250*	160 to 300	0	2
> 250 < 500†	80 to 300	4	6
> 500	80 to 500	3	3

* One to two courses. † Three to four courses.

Table 3. Methotrexate treatment, conceptions, and wasted fetuses.

Dosage (mg)	Conceptions (No.)	Wasted fetuses	
		No.	%
100 to 250	32	5	16
250 to 500	39	9	23
> 500	16	2	12
None	1	1	100

cent of children from normal pregnancies had various congenital defects, with 10 percent requiring special medical and educational services. Sixty-eight children in our series are 2 years of age or older and are, therefore, at greater risk for the recognition of a congenital defect, yet only two children required long-term medical care, one for tetralogy of Fallot and one for bilateral nerve deafness. Ekelund *et al.* (*5*) found an incidence of minor malformations of 9.6 percent and of major malformations of 3.3 percent in a recent prospective study of over 6200 children followed to age 1 year.

It is interesting to speculate on the apparent absence of any significant increased risk to mother or fetus in this study. The human fetus is most susceptible to teratogenic agents such as rubella, toxoplasmosis, irradiation, and other agents or forces during the first trimester. None of our patients was treated while pregnant, and pregnancy was proscribed for one full year following exposure to these agents.

There are many data that would suggest that methotrexate and actinomycin-D are most effective during cellular DNA synthesis. Cells in a "resting stage" are relatively resistant to these agents. The 1-year period of forced contraception may allow the more mature and possibly defective ova to be wasted. It is also possible that only oocytes in a developing follicle are active enough metabolically to be damaged and that a year of contraception allows only previously inactive and immature oocytes and follicles to persist and produce the gametes for subsequent reproduction.

There is a possibility that mutations due to chemotherapy were present but undetected in the products of the pregnancies of our patients. Most mutations are recessive and, therefore, are not easily detected unless the trait is sex-linked and thus occurs with greater frequency in male offspring. Observations over several generations would be required to answer this question.

The aborted fetuses in our series were not reported as abnormal, but no systematic examinations were undertaken.

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Repression of Colony Formation Reversed by Antiserum to Mouse Thymocytes

Abstract. *Marrow cells derived from C57BL/6 mice form many fewer splenic colonies in irradiated C57BL/6 × C3H F1 hybrid recipients than in irradiated C57BL/6 recipients (repression of colony formation). This effect is reversed by treatment of the hybrid recipients with active antiserum to mouse thymocytes. The repression phenomenon cannot readily be explained in immunological terms; hence the effect of the antilymphocyte serum on this phenomenon may not result from immunosuppression in the usual sense.*

Normal (*1, 2, 3*) or malignant (*4*) cells are known to grow less well in F1 hybrid recipients than in isologous hosts. This phenomenon has been called CFU (colony forming unit) repression (*1*), hybrid resistance (*2*), or allogeneic inhibition (*5*). Cudkowicz and Stimpfling (*2, 6*) have provided evidence that the phenomenon can result from heterozygosity at a genetic site closely linked to the D subregion of the histocompatibility-2 (H-2) locus. The mechanism of the repression effect is unknown, but attempts to explain it in terms of immunological phenomena associated with transplantation, such as ordinary host-versus-graft reactions, have not been widely accepted (*1, 5, 7*). We have suggested that the defective growth of marrow transplants in this situation may be a reflection of failure of a control mechanism that normally regulates cellular proliferation through gene products existing as cell surface components (*8*). To test this hypothesis, we have studied the effects of a number of agents on the formation of splenic colonies by C57BL/6 marrow stem cells injected into irradiated C57BL/6 × C3H F1 hybrid mice. An active horse antiserum to mouse thymocytes (ALS; antilymphocyte serum) is highly effective in improving the efficiency of colony formation in this donor-host combination.

Two different preparations of horse antiserum to mouse thymocytes were used, one nonactive (ALS-A) and one active (ALS-B) in tests for immunosuppressive effect (*9*). Female (C57BL/6 × C3H F1) mice received 0.5 ml of either ALS-A or ALS-B intraperitoneally. One day later they were given 900 rad of ^{137}Cs gamma radiation followed by intravenous injection of known numbers of C57BL/6 marrow cells. The animals were killed 9 days later, their spleens were removed and fixed in Bouin's solution, and the number of macroscopic splenic colonies was determined (*10*).

When C57BL/6 marrow cells are injected into heavily irradiated C57BL/6 × C3H F1 mice, the efficiency of colony formation is only 1 to 10 percent of that observed when the same cells are transplanted into isologous irradiated C57BL/6 hosts (*1*) (Fig. 1). When varying numbers of C57BL/6 marrow cells were injected into irradiated female C57BL/6 × C3H F1 hosts 24 hours after treatment with nonactive ALS-A, full repression of colony formation was still seen, similar to that observed in irradiated C57BL/6 × C3H F1 mice that received no serum (Fig. 1). In contrast, complete elimination of the repression effect was achieved by treatment of the irradiated C57BL/6 × C3H F1 hosts with ALS-B 1 day prior to transplantation of C57BL/6 marrow cells. Not only was the efficiency of colony formation in the hosts treated with active serum similar to that observed in isologous hosts (Fig. 1), but the size of the individual colonies in the spleens of hosts treated with active serum was much larger than that in hosts treated with inactive serum (Fig. 1). Colonies from recipients treated with active ALS-B when examined histologically contained erythropoietic and granulopoietic cells similar